Hair Cells and Spiral Ganglion Neuron Differentiation from Human Embryonic Stem Cells

Grant Award Details

Hair Cells and Spiral Ganglion Neuron Differentiation from Human Embryonic Stem Cells

Grant Type: SEED Grant

Grant Number: RS1-00453

Investigator:

Name:	Ebenezer Yamoah
Institution:	University of California, Davis
Type:	PI

Disease Focus: Hearing Loss

Human Stem Cell Use: Embryonic Stem Cell

Award Value: $458,071

Status: Closed

Progress Reports

Reporting Period: Year 2

View Report

Grant Application Details

Application Title: Hair Cells and Spiral Ganglion Neuron Differentiation from Human Embryonic Stem Cells

Public Abstract:

Hair cells (HCs) convert sound and balance signals into electrical impulses in the inner ear, including the cochlea and the vestibular endorgans, with remarkable precision and sensitivity. Our long-term goal is to stimulate HC regeneration in human inner ears and to enable the functional innervations of HCs by neurons. Hair cells are terminally-differentiated cells. Once HCs are lost due to noise, ototoxic drugs or aging, there is no effective way to stimulate HC regeneration in mature inner ears. However, recent studies from our group and others have demonstrated very encouraging results: new HCs may be formed from stem cells.

We know very little about how to induce HC regeneration in a mature sensory epithelia in the auditory and vestibular organs. Indeed, determination of the mechanisms of induction of HCs and the assembly of the functional machinery of HCs in the mature cochlea has direct relevance to our understanding of how a HC may be derived from specific human embryonic stem cells (hESCs). Strong evidence from data in developmental cell biology and electrophysiology motivates our hypothesis that the specific factors regulating HC differentiation interact to confer their functions and that specific hESC-types have the potential to differentiate into HCs and their innervating neurons. We further predict that newly differentiated HCs assemble their transduction apparatus and ionic currents in a coordinated fashion to achieve the cell's sensitivity.

The proposed research will identify some of the candidate proteins and their mechanisms of interactions that are required to induce HC differentiation from hESCs. The project will determine the hESC-types, which have the competence to transform into HCs. We will assess whether a HC assembles its entire transduction apparatus and ionic conductance simultaneously, at a specific stage in the process of differentiation, or whether the assembly of the final apparatus entails multiple steps during maturation. Moreover, these studies should reveal how HCs and neurons coordinate and regulate the mechano-electrical apparatus, information that might be exploited to induce regeneration and functional transduction apparatus assembly from hESCs after HC damage.

Of particular importance to auditory and vestibular science is the possibility that a rational design of a cocktail of protein/factors may be assembled for 'biological implants', as our understanding of the mechanisms of regeneration of HCs becomes more refined. Since the mechanisms used by the internal ear and hESCs may be expressed in different forms by other signal transduction systems, these studies may provide novel insights into such areas as protein-protein interaction, cell proliferation, developmental processes, and hESC signaling in general.

Statement of Benefit to California:	One common sign of aging is a decline in hearing function, which results from genetic and environmental factors (e.g. congenital disorders and exposure to ototoxic drugs). Indeed, 3 in 1,000 children are born with congenital deafness and 30-50% of the California population will develop hearing loss with age, and the same proportion of people will have vestibular disorders that may lead to hip or serious fractures. Our perception of sound and balance relies on the exquisite sensitivity of hair cells (HCs) in the inner ear. Hair cells are terminally-differentiated cells. Once HCs are lost due to noise, ototoxic drugs or aging, there is no effective way to stimulate HC regeneration in mature inner ears. Deafness is an insidious communication problem that affects our population. Hellen Keller once wrote “Blindness cuts us off from things, but deafness cuts us off from people”. We have obtained data that strongly suggests that specific human embyonic stem cells (hESCs) may be a potential source to derive new HCs and neurons that innervate them for “biological implantation” in humans in the future. The proposed research will identify some of the candidate proteins and their mechanisms of interactions that are required to induce HC and neuronal differentiation from hESCs. The project will determine the hESC-types, which have the competence to transform into HCs and neurons. We will assess whether HCs and neurons assemble their entire transduction apparatus and ionic conductances simultaneously, at a specific stage in the process of differentiation, or whether the assembly of the final apparatus entails multiple steps during maturation. Moreover, these studies should reveal how HCs and neurons coordinate and regulate the mechano-electrical apparatus, information that might be exploited to induce regeneration and functional transduction apparatus assembly after damage.